IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Atty Docket: OP DEN CAMP-1

In re application of:	Art Unit: 1652
Hubertus J. M. OP DEN CAMP *et al.*	Examiner: Christian L. Fronda
Serial No. 10/500,872	Washington, DC
Filed: July 7, 2004	December 24, 2008
For: TRANSFORMED EUKARYOTIC CELLS THAT DIRECTLY CONVERT XYLOSE TO XYLULOSE	Confirmation No. 1317

DECLARATION OF JOHANNES PIETER VAN DIJKEN PURSUANT TO 37 C.F.R. § 1.132

Assistant Commissioner for Patents
Randolph Building
401 Dulany Street
Alexandria, VA 22314

Dear Sir:

I, the undersigned, declare as follows:

1. I am a Professor of Biotechnology at the Delft University of Technology, The Netherlands, and the general director of Bird Engineering BV (a contract research biotechnology company). I have worked in the field of microbiology and biotechnology since the early 1970's. I have published over 130 papers in this field. A brief version of my Professional Résumé and list of publications is attached to this Declaration as Appendix 1. I consider myself to be an expert in the field of this invention.

2. I am familiar with this patent application and have read and understand the latest Office Action and the references cited by the Examiner in rejecting the pending claims. My primary purpose here is to discuss the unobviousness of the present claims in relation to the cited references. Claim 1 (and various dependent claims) were considered obvious based on either of two references combined with a published sequence.

(a) a patent to Guan *et al.* US Patent 5,643,758 ("Guan" below); or

(b) Karlsson *et al.* (*Eur J Biochem.* 2001, *268*:6498-6507 ("Karlsson" below).

The published sequence appears in EMBL record of a deposited xylose isomerase ("XI") gene, Accession No. Q9P8C9, encoding the protein of SEQ ID NO:1.[1]

3. I wish to address in particular how the successful use of this XI gene, as first shown in the present invention, was unexpected, particularly when considering the recognized need (which up until the time of the invention had not been realized) for a way to exploit lignocellulosic feedstocks that contain appreciable amounts of the wood sugar xylose (vs. glucose) as a more economical carbon source for producing ethanol (as well as certain non-ethanolic fermentation products). In this context I point out that I and my co-workers hypothesized as early as 1983 the desirability of introducing xylose isomerase activity into yeast (P.M. Bruinenberg, P.H.M. de Bot, J.P. van Dijken and W.A. Scheffers, "The role of redox balances on the anaerobic fermentation of xylose by yeasts," *Eur. J. Appl. Microbiol. Biotechnol. 18*:287-92 (1983) (copy being provided). However, despite this, a long history of failures followed. See, Section 5 below and the Gardonyi reference cited there, as well as Section 8.

4. I understand that the Patent Office rejected the claims based on the Guan and Karlsson, on the following basis: The references were described as differing from the invention in that the yeast cells (or cells of the filamentous fungus *Trichoderma reesei*) in the references were **not** transformed with DNA encoding the XI of amino acid sequence SEQ ID NO:1. (Neither did these documents describe cells transformed with a sequence that is at least 95% identical with this sequence.) However, SEQ ID NO:1 (or one 99% identical to it) was known to the present inventors' and colleagues who put it into the UniProtKB/TrEMBL database as Accession Q9P8C9 and made it public. However, this did not suggest that this sequence could be used in the present invention.

5. The Patent Office believes that the transformation of yeast cells (per Guan) or *Trichoderma reesei* cells (per Karlsson) with the specific nucleic acid encoding the XI disclosed in the Q9P8C9 database record would have been obvious at the time this invention was made. The Examiner contends that a skilled scientist working in this field would have been **motivated** to do this due by a generalized desire "to express and purify" the XI of Accession Q9P8C9. Further, the Examiner concluded that it would have been **reasonable to expect success** in

[1] Or more precisely, that the Office Action states is 99% identical to SEQ ID NO:1. I am a co-author of the reference shown this EMBL record.

achieving this goal merely because recombinant DNA technology was at an "advanced state" when it came to expression and purification of heterologous or homologous proteins. If one concedes that there is an "automatic" motivation to recombinantly express **any** disclosed DNA sequence in order to purify the protein product, just because the DNA sequence is known, then I might concede that there would be motivation to make and purify more of this XI protein. But, as discussed below, this is not the present invention. The Examiner seems to be oversimplifying the reality by simply combining Guan and Karlsson with the DNA sequence encoding the XI of Accession Q9P8C9 (99% identical to SEQ ID NO: 1) and concluding that recombinant expression and purification of this XI sequence is "the **predictable** result of the recombinant expression and purification of xylose isomerase taught by Accession Q9P8C9" (when this is combined with Guan and Karlsson) However, that assumes that it is trivial to express the XI protein --for whatever purpose, let alone to have it function inside the cells so that a metabolic alteration can be exploited. It might be trivial in certain situations. However, the history of the developments leading to this invention teach otherwise. One additional reference that points out the failed attempts to functionally express XI in yeast is Gardonyi, M and Hahn-Hägerdal, B: "The *Streptomyces rubiginosus* xylose isomerase is misfolded when expressed in *Saccharomyces cerevisiae*" *Enz. Microb. Technol. 32:*252-259 (2003); copy being provided). While I recognize that this paper (reporting another failure) was published shortly after the filing date of the present application, it does provide a convenient summary of the history of failed earlier attempts (prior to the present invention).

The Examiner states the following:

- *"Recombinant expression and purification of proteins have the recognized, well-established advantage of production of large, purified amounts of the desired proteins."*

  I do not dispute this statement – only the lack of its applicability to the present situation.

- *"Use of yeast cells is well-known for recombinant expression and purification of desired proteins."*

  I do not dispute this statement – only the lack of its applicability to the present situation.

- *"The knowledge of persons of ordinary skill in the field of recombinant expression and purification of proteins in eukaryotic cells such as yeast and the means of optimizing this expression and purification (purportedly based on the mere combination of the 3 references) when coupled with the inventors' first showing of successful expression of XI (SEQ ID NO: 1) in yeast cells, are proof that there would have been a "reasonable expectation of success" in making this invention."*

  I strongly disagree with this reasoning and conclusions, as I discuss below.

6. First, as already pointed out to the Patent Office, a significant number of XI sequences were known at the time of the invention. See, for example, Harhangi, HR *et al.*, 2003, *Arch. Microbiol. 180*:134-141; of record[2]), particularly Fig. 4A (showing a subset of all known XI genes at the time). To date, some 450 XI sequences are publicly available. I know of no specific motivation to select a single one, namely SEQ ID NO:1 (or a homologue with 95% sequence identity with it), particularly since this sequence is more closely related to XI sequences **known not to function in yeast,** such as, *e.g.*, the *E. coli* XI, of Chan *et al.* 1989 (*Appl. Microbiol, Biotechnol. 31*:524–28; copy being provided), than to the thermophilic XI's that show at least some activity in yeast (see below under Sec. 8).

7. The Examiner seemed to focus on ramped-up production of the XI protein for purification. Given the known difficulty in expressing exogenous XI's in eukaryotic cells, including yeast (see below under Sec. 8), I dispute whether even this conclusion is true. However, this is not what the inventors are doing. This invention concerns metabolic engineering, not recombinant protein production/purification. Metabolic engineering is the introduction of new metabolic pathways into a microorganism or other cell. In this particular case, the enzyme XI is an essential component of this new (in the case of yeasts) pathway. Such introduction of new pathways into cells is also referred to as "synthetic biology." To that end, the claims (reflected in amended (new) claim 41) require that the cell be transformed with a particular XI DNA that is characterized structurally by parts (i) (B)-(E) of the claim. Moreover, this coding sequence must be operatively linked to an appropriate promoter so that the XI is expressed. Even further, this expression must result in a functional protein (under "reasonable" and "practical" conditions of cell growth and fermentation) that confer on the cell the ability to convert xylose to xylulose. The same limits do not apply when one is simply purifying large quantities of protein because for such purposes, initially obtaining the protein in a denatured state, or denaturing it by the purification scheme, may be acceptable.

8. More important, however, are the Patent Office's conclusions about there being a reasonable expectation of success. I focus on the patent application's description (page 2, line 26 to page 3, line 10) of how most available XI genes known at that time, from a number of bacterial sources, for which expression in yeast had been attempted, had failed to produce active XI. See, for example, Chan *et al.*, *supra*, who expressed *E. coli* XI in the yeast *S. pombe* and

[2] and of which I am a co-author

obtained inadequate levels of XI activity. See, also, Amore *et al.*, 1989, *Appl. Microbiol, Biotechnol. 30*:351-357 (copy being provided), who expressed *B. subtilis* XI in *S. cerevisiae* and found that while as much as **5%** of total cell protein was XI, it lacked any XI enzymatic activity. As I indicated Section 5 above, the Gardonyi *et al.* reference summarizes further failed attempts to express functional XI in yeast up until the present invention was made. Although two XIs from thermophilic bacteria expressed in *S. cerevisiae* showed a specific activity of 1 μmol/min/mg, this occurred only at 85°C (the "normal" temperature for the gene "donor"). However, these are highly unphysiological temperatures for common eukaryotic cells (*e.g.*, *S. cerevisiae* grow at 20-35°C). At these lower "acceptable" temperatures, "only a few percent of this activity is left, which is not sufficient for efficient alcoholic fermentation from xylose."

Therefore, even taking into account the Guan and Karlsson references, there still remained a large gap, which was not bridged until the present inventors discovered XI genes that would be expressed in yeast (or other eukaryotic cells) under growth and metabolic (*i.e.*, physiological) conditions that would enable the cells to grow on xylose rather than glucose as a carbon source.

One must also keep in mind that the claimed XI sequence (SEQ ID NO:1 or one that is 95% identical) is a protein with certain defined characteristics that should have been closer to proteins from conventional bacteria (*e.g.*, *Bacillus, E. coli and Streptomyces*). However, XI genes from such sources could not be actively expressed in yeast while, unexpectedly, the claimed XI sequence could.

Therefore, I must conclude based on my experience and familiarity with the present technology that there would NOT have been any reasonable expectation of success in expressing the claimed XI in active form in a eukaryotic cells, such as yeast or a fungus, under conditions that would permit the cells to metabolize xylose to xylulose and thus use xylose as their sole carbon source.

9. The Patent Office has listed six "exemplary rationales" that may support a conclusion of obviousness. My rejoinder to these is provided below.

(A) "*Combining prior art elements according to known methods to yield predictable results*"

While the methods used in this invention were known, the results (as discussed) were certainly not predictable, notwithstanding the Examiner's opinion.

(B) "*Simple substitution of one known element for another to obtain predictable results*"

While it may have seemed to be this "simple," when people began seeking an XI that could be used to grow yeast on xylose, it certainly was not the case, as borne out by the history of failed attempts (also set out in the application with multiple citations).

(C) "*Use of known technique to improve similar devices (methods, or products) in the same way*"

While the techniques used in constructing the transformed cells of this invention may have been "known,", the success of the "products" (modified cells) were highly unexpected.

(D) "*Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results*"

The improved product and process (here), though long sought, went through a lengthy and arduous path until the present invention provided the first successful "improvement." The results, even if desired, were certainly not predictable.

(E) *"Obvious to try" - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success"*

As discussed, although people had a list of XI genes (admittedly "finite") to "try" in the quest for the present results, none of them worked, and no one knew why. Finding the right XI gene was anything but "predictable" and, as it turned out, there was no reasonable expectation that any particular XI would bring success.

(F) "*Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art*"

Here, there was no assistance from work in this or another field that suggested the solution that the inventors achieved. The "variations" (*i.e.*, which XI sequence may or may not work), presented a wall of unpredictability that only the present inventors, not the combination of cited references, breached.

(G) *Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.*

Nothing that was tried prior to this invention provided an appropriate suggestion of what would work, even if the desire was there to try to achieve the inventors' result.

10. In summary, the Examiner's conclusions about obviousness, in my opinion, appear to based on assumptions and concepts that do not fit the present situation. Considering the well-described history of failure in this field, the inventors' success was a highly unobvious achievement in an area where everything pointed away from a path to success until this invention was made.

11. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to by true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Date: December 23, 2008 /s/ Johannes van Dijken

Johannes van Dijken

Appendix 1

Brief CV of Johannes Pieter van Dijken

Delft University of Technology
Julianalaan 67
2628 BC Delft
The Netherlands
J.P.vanDijken@tudelft.nl

Born: 12-June-1949, Assen, The Netherlands

Education

1966-1972	M.Sc in Biology/Biochemistry, University of Groningen, The Netherlands *(cum laude)*
1972-1976	PhD in Microbiology, University of Groningen Thesis: Oxidation of Methanol by Yeasts. (Research funded by Shell Sittingbourne, UK)

Professional Career

1976-1977	Post-doctoral fellow, University of Sheffield (UK) Prof. J.R. Quayle FRS.
1977-1980	Post-doctoral fellow, University of Groningen, The Netherlands Microbial physiology of methylotropic microorganisms and the cytochemistry/electron microscopy of yeasts; Prof. W. Harder.
1980-2001	Associate Professor, Department of Biotchnology Delft University of Technology, The Netherlands (initially in "Yeast Physiology Group") Member: Kluyver Laboratory of Biotechnology (now Kluyver Centre for Genomics of Industrial Fermentation)
2002-present	Professor of Biotechnology, Delft University of Technology
1989-present	Co-founder and General Director, of Bird Engineering BV (The Netherlands) A biotechnology company that performs contract research for national and multinational corporations

Other Activities

- Highly cited scientist in his discipline.
- Published over 130 papers in peer-reviewed journals (partial publication list attached)
- Inventor/Co-inventor on 7 patents
- Member of the International Commission on Yeasts
- Invited speaker and/or Chairman of several international symposia
- Scientific consultant to Avebe, Unilever, Heineken, Tate and Lyle, DSM, Mascoma, Amyris

Appendix 1

PARTIAL LIST OF PUBLICATIONS BY J.P. VAN DIJKEN

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5: Engineering NADH metabolism in Saccharomyces cerevisiae: formate as an electron donor for glycerol production by anaerobic, glucose-limited chemostat cultures.
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6: Alcoholic fermentation of carbon sources in biomass hydrolysates by Saccharomyces cerevisiae: current status.
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9: The Low Biomass Yields of the Acetic Acid Bacterium Acetobacter pasteurianus Are Due to a Low Stoichiometry of Respiration-Coupled Proton Translocation.
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10: Enzymic analysis of NADPH metabolism in beta-lactam-producing Penicillium chrysogenum: presence of a mitochondrial NADPH dehydrogenase.
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11: Use of the yeast Hansenula polymorpha (Pichia angusta) to remove contaminating sugars from ethyl beta-D-fructofuranoside produced during sucrose ethanolysis catalysed by invertase.
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12: Evolutionary engineering of mixed-sugar utilization by a xylose-fermenting Saccharomyces cerevisiae strain.
Kuyper M, Toirkens MJ, Diderich JA, Winkler AA, van Dijken JP, Pronk JT.
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van Maris AJ, Winkler AA, Porro D, van Dijken JP, Pronk JT.
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